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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/709,170	11/10/2000	Raymond P. Warrell	10412-025	4982

20583 7590 07/17/2002

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EXAMINER	
GIBBS, TERRA C	

ART UNIT	PAPER NUMBER
1635	13

DATE MAILED: 07/17/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/709,170	WARRELL ET AL.	
	Examiner	Art Unit	
	Terra Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-33 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-33 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-33 are pending in the instant application.

Information Disclosure Statement

The information disclosure statement filed, November 10, 2000 has been placed in the application file, but the information referred to therein has not been considered. It is noted that applicant has indicated that all references were submitted, however, no references could be located in the application. Applicant is asked to resubmit all the references contained in the information disclosure statement so that they can be considered.

Claim Rejections - 35 USC § 112

Claims 1-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of *treating* cancer in a human via bcl-2 antisense therapy, does not reasonably provide enablement for a method of *preventing* cancer in a human via bcl-2 antisense therapy. The specification as filed does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 1-23 are drawn to or embrace a method of treating or preventing cancer in a human via bcl-2 antisense therapy.

The instant invention specification provides general methodologies for a method of treating cancer in a human via bcl-2 antisense therapy.

The specification as filed does not provide adequate guidance of examples that would show by correlation the practice of the instant invention without the need for undue trial and error experimentation.

The prior art (see art rejection below) provide ample evidence for treatment of rumors via bcl-2 antisense, but does not show the prevention of cancer or how one would prevent cancer via bcl-2 antisense. The instant specification does not show more than the prior art, therefore, one is left with undue trial and error experimentation to practice the instant invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5, 13-18, 24-28 and 31-33 are rejected under 35 U.S.C. 102(b) as being anticipated by Webb et al., (The Lancet, 1997 Vol 349:1137-1141).

Claims 1-5, 13-18, 24-28 and 31-33 are drawn to or embrace a method of treating cancer in a human comprising administering a bcl-2 antisense oligonucleotide at a dose of 0.01 to 50 mg/kg/day for a period consisting of 2 to 13 days.

Webb et al. disclose a daily subcutaneous infusion of a fully phosphorothioated bcl-2 antisense administered for 2 weeks to nine patients with non-Hodgkin's lymphoma (see page

1137, Methods). Webb et al. further disclose the daily dose of bcl-2 antisense was increased incrementally from 4.6 mg/m^2 to 73.6 mg/m^2 for 14 days (see page 1137, Findings)

Claims 1-5, 13-18, 24-28 and 31-33 are rejected under 35 U.S.C. 102(a) as being anticipated by Waters et al.,(Journal of Clinical Oncology, 2000 Vol 18:1812-1823).

Waters et al. disclose phase I clinical and pharmacokinetic study of bcl-2 antisense oligonucleotide therapy in patients with non-hodgkin's lymphoma. Waters et al. further disclose eight cohorts of patients received doses between 4.6 and 195.8 mg/m^2/day for 14 days by subcutaneous infusion.

Claims 1-5, 13-18, 24-28 and 31-33 are rejected under 35 U.S.C. 102(b) as being anticipated by Morris et al., (Proceedings of the American Society of Clinical Oncology, 1999 18:323a).

Morris et al. disclose continuous intravenous infusion of bcl-2 antisense, G3139, at doses of 0.6, 1.3, 1.7 and 2.3 mg/kg/day for 14 days (see Abstract) in patients with advanced solid tumors.

Claims 1-6, 9-12, 13-19, 24, 26-29 and 31-33 are rejected under 35 U.S.C. 102(b) as being anticipated by Jansen et al., (Proceedings of the American Society of Clinical Oncology, 1999 19:531a).

Claims 1-6, 9-12, 13-19, 24, 26-29 and 31-33 are drawn to or embrace a method of treating cancer in a human comprising administering a bcl-2 antisense oligonucleotide at a dose of 0.01 to 50 mg/kg/day for a period consisting of 2 to 13 days, in combination with a cancer therapeutic agent.

Jansen et al. disclose the intravenous infusion of bcl-2 antisense, G3139, at doses of 0.6, 1.3, 1.7, and 2.3 mg/kg/day for 14 days, in combination with therapeutic agent, dacarbazine, in patients with advanced malignant melanoma (see Abstract).

Claims 1-6, 9-12, 13-19, 24, 26-29 and 31-33 are rejected under 35 U.S.C. 102 (a) as being anticipated by Jansen et al., (The Lancet, 2000 Vol 356:1728-33).

Jansen et al. disclose the intravenous infusion of bcl-2 antisense, G3139, at doses of 0.6, 1.3, 1.7, and 2.3 mg/kg/day for 14 days, in combination with therapeutic agent, dacarbazine (at up to 1000 mg/m^2 per cycle), in patients with advanced malignant melanoma (see page 1137, Methods and Figure 3).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-33 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Raynaud et al., (Journal of Pharmacology and Experimental Therapeutics, 1997 Vol 281:420-427) in further view of Lopes de Menezes et al., (Clinical Cancer Research, 2000 Vol. 6:2891-2902), Miayake et al., (Journal of the National Cancer Institute, 2000 Vol 92:34-41), Cotter et al., (Biochimica et Biophysica Acta, 1999 Vol 1489:97-106) Webb et al. (The Lancet, 1997 Vol 349:1137-1141) and Bennett et al. [U.S. Patent No: 6,214,986].

Claims 1-33 are broadly drawn to a method of treating cancer in a human comprising administering a bcl-2 antisense oligonucleotide at a dose of 0.01 to 50 mg/kg/day for a period consisting of 2 to 13 days, in combination with a cancer therapeutic agent.

Raynaud et al. have taught the pharmacokinetics of bcl-2 antisense, G3139, (100 μg) (approximately 5 mg/kg) after single i.v. bolus administration or s.c. infusion for 1 week in BABL/c mice (see Abstract, and page 421, first paragraph). Raynaud et al. also teach an oligonucleotide of SEQ ID NO: 17 of the instant invention (see page 35).

Lopes de Menezes et al. have taught the molecular and pharmacokinetic properties associated with the therapeutics of bcl-2 antisense oligonucleotide, G3139, combined with free and liposomal chemotherapy agent, doxorubicin in SCID mice. Lopes de Menezes et al. have further taught *in vivo* antitumor activity of G3139 (5 or 10 mg/kg) given on days 3-7, 10-14 and 17-21 (see page 2893, last paragraph and Figures 1A and B) in breast tumor bearing mice. Lopes de Menezes et al. have further taught doxorubicin (5 or 10 mg/kg; 1, 3, or 6 injections once a week) was concurrently administered i.v. via the tail vein in conjunction with bcl-2

antisense oligonucleotides (see page 2893, second column). Lopes de Menezes et al. also teach an oligonucleotide, which contains all of the structural limitations of SEQ ID NO: 17 of the instant invention (see page 2892, last paragraph). Lopes de Menezes et al. assert that although the bcl-2 antisense, G3139, can cause effective reductions in tumor cell bcl-2 protein levels that lead to increased antitumor activity, its therapeutic utility may depend on various aspects of tumor physiology in addition to the pharmacological properties of anticancer drugs with which it may be combined (see page 2901, last paragraph).

Miayake et al. have taught adjuvant *in vivo* administration of antisense Bcl-2 oligonucleotides and micellar paclitaxel administration following castration in Shionogi tumor bearing mice (see Abstract and page 39). Miayake et al. further disclose bcl-2 antisense (12.5 mg/kg body weight) was injected intraperitoneally once daily for 14 days and 0.5 mg of micellar paclitaxel was injected intravenously once daily for 5 days (see Figures 4A, 4B and 5A). Miayake et al. assert that the inhibition of bcl-2 function with the use of antisense oligonucleotides, plus paclitaxel, causes a delay in progression to androgen independence as well as inhibition of established androgen-independent tumor growth in the Shionogi tumor model. Miayake et al have taught paclitaxel (Taxol) treatment following administration of bcl-2 antisense (see Figure 4). Miayake et al. further teach clinical studies with bcl-2 antisense plus paclitaxel for patients with prostate cancer (see page 40, last paragraph).

Raynaud et al., Lopes de Menezes et al. and Miayake et al. do not teach a method of treating cancer in a human.

Cotter et al. and Webb et al. teach a method of treating cancer in a human.

Cotter et al. teach a review of bcl-2 antisense oligonucleotide, G3139, preclinical studies, pharmacokinetics and toxicities (see pages 98-99). Cotter et al. further teach and review a phase I bcl-2 antisense therapy in lymphoma (see page 100).

Webb et al. teach the first study of bcl-2 antisense therapy in human beings (see entire article, especially page 1137, Background). Webb et al. have taught that bcl-2 antisense, when administered before chemotherapy, may have a sensitizing effect (see page 1141, last paragraph).

Cotter et al. and Webb et al. do not teach cancer therapeutics dosages.

Bennett et al. teach cancer therapeutics dosages.

Bennett et al. have taught "the formulation of therapeutic compositions and their subsequent administration is believed to be within the skill of those in the art. Dosing is dependent on severity and responsiveness of the disease state to be treated, with the course of treatment lasting from several days to several months, or until a cure is effected or a diminution of the disease state is achieved. Optimal dosing schedules can be calculated from measurements of drug accumulation in the body of the patient. Persons of ordinary skill can easily determine optimum dosages, dosing methodologies and repetition rates. Optimum dosages may vary depending on the relative potency of individual oligonucleotides, and can generally be estimated based on EC_{50s} found to be effective in *in vitro* and *in vivo* animal models. In general, dosage is from 0.01 μg to 100 g per kg of body weight, and may be given once or more daily, weekly, monthly or yearly, or even once every 2 to 20 years. Persons of ordinary skill in the art can easily estimate repetition rates for dosing based on measure residence times and concentrations of the drug in bodily fluids or tissues" (see columns 16-17, last and first paragraphs, respectively).

In view of Raynaud et al., Lopes de Menezes et al., Miayake et al., Cotter et al., Webb et al. and Bennett et al., it would have been obvious to devise a method of treating cancer in a human comprising administering to said human, a bcl-2 antisense oligonucleotide in one or more cycles of therapy at a dose of 0.01 to 50 mg/kg/day for a period consisting of 2 to 13 days in combination with or without a cancer therapeutic agent. One of ordinary skill in the art would have been motivated to devise a method of treating cancer in a human since the prior art has indicated the desirability of human bcl-2 antisense therapies for lymphomas (Cotter et al. and Webb et al.). One of ordinary skill in the art would have been motivated to make antisense oligonucleotides to bcl-2 and had a reasonable expectation of success since the art taught the use of bcl-2 oligonucleotides as therapeutic agents against cancer (Raynaud et al., Lopes de Menezes et al. and Miayake et al.). One of ordinary skill in the art would have been motivated to coadminister a cancer therapeutic with the bcl-2 antisense oligonucleotide since Raynaud et al. teach the therapeutic utility of the antisense may depend on various aspects of tumor physiology in addition to the pharmacological properties of anticancer drugs with which it may be combined. One of ordinary skill in the art would have been further motivated to coadminister a cancer therapeutic with the bcl-2 antisense oligonucleotide since Miayake et al. assert clinical studies with bcl-2 antisense plus paclitaxel for patients with prostate cancer. One of ordinary skill in the art would have been motivated to administer a specific dose of a cancer therapeutic agent and had a reasonable expectation of success since Bennett et al. have taught persons of ordinary skill can easily determine optimum dosages, dosing methodologies and repetition rates.

The invention as a whole would therefore have been obvious to one of ordinary skill in the art at the time the invention was made.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is (703) 306-3221. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

tcg
July 11, 2002

SEAN McGARRY
PRIMARY EXAMINER
1635